UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,432	10/03/2006	Gregory D. Plowman	EX03-078C-US	4479

20306 7590 06/22/2009

MCDONNELL BOEHNEN HULBERT & BERGHOFF LLP
300 S. WACKER DRIVE
32ND FLOOR
CHICAGO, IL 60606

EXAMINER	
CANELLA, KAREN A	

ART UNIT	PAPER NUMBER
1643	

MAIL DATE	DELIVERY MODE
06/22/2009	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/532,432	PLOWMAN ET AL.	
	Examiner	Art Unit	
	Karen A. Canella	1643	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2009*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-13, 15-22, 24-31, 34, 35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *15,16,24,25,34 and 35* is/are allowed.

6)☒ Claim(s) *1-13, 17-22, 26-31* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Claims 14, 23, 32 and 33 have been canceled. claims 1-13, 15-22, 24, 25 and 27-31 have been amended. Claims 1-13, 15-22, 24-31, 34 and 35 are pending and under consideration.

It is noted that MAP2K6 is synonymous with MEK6, MKK6, PRKMK6, mitogen activated protein kinase kinase-6.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claim 1 is rejected under 35 U.S.C. 102(b) as being anticipated by Wong et al (Gynecologic Oncology, August 2001, Vol. 82, pp. 305-311).

Claim 1 is drawn to a method comprising (a)providing an assay system comprising a MAP2K6 polypeptide or nucleic acid, (b) contacting the assay system with a test agent under conditions whereby, but for the presence of the test agent, the system provides a reference activity and (c)detecting a test agent-biased activity of the assay system. Claim 5 embodies the method of claim 1, wherein the assay system comprises an expression assay and the candidate test agent is a nucleic acid modulator.

Claim 31 is drawn to a method for diagnosing a disease in a patient comprising (a)obtaining a biological sample from a patient, (b) contacting the sample with a probe for a modulator of branching morphogenesis. Claim 32 embodies the method of claim 31 wherein said disease is cancer.

Wong et al disclose a method comprising measuring the expression level of MAP2K6 polynucleotides normal, pre-neoplastic and neoplastic ovarian cell lines and ovarian surface epithelial cells obtained from patients(page 306, under the heading of "Cells and Cell Lines" in the presence and absence of hepatocyte growth factor (HGF) (Figure 1). .

It is noted that the recitation of a method "of identifying a candidate branching morphogenesis modulating agent" and a "method for diagnosing a disease in a patient" has not

been given patentable weight because said recitations occur in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone. See In re Hirao, 535 F.2d 67, 190 USPQ 15 (CCPA 1976) and Kropa v. Robie, 187 F.2d 150, 152, 88 USPQ 478, 481 (CCPA 1951).

It is further noted that the phrase "wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent" are not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

Further, steps (c) and (d) are not given patentable weight as they are confined to mental steps, rather than to active method steps

Given that the method of the prior art comprises the same method steps as claimed in the instant invention, the claimed method is anticipated because the method will inherently be a method for identifying a candidate branching morphogenesis modulating agent and a method for diagnosing a disease in a patient. See Ex parte Novitski 26 USPQ 1389 (BPAI 1993).

Applicant argues that in order to anticipate the instant invention, Wong must teach a method of identifying a candidate branching morphogenesis modulating agent comprising the steps of providing an assay system comprising a MAP2K6 polypeptide or nucleic acid and contacting said assay system with a candidate composition under conditions wherein the presence of the test agent provides a reference activity and detecting the reference activity, wherein a difference between the test agent biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent. This has been considered but not found persuasive. As stated above,

the recitation of a method "of identifying a candidate branching morphogenesis modulating agent" and a "method for diagnosing a disease in a patient" has not been given patentable weight because said recitations occur in the preamble. A preamble is generally not

accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.

Further, as stated above,

the phrase "wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent" are not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited.

Applicant further argues that Wong merely teaches the determination of levels of MEK6 in ovarian cancer cells. This has been considered but not found persuasive. As stated above, Wong teaches a method comprising measuring the expression level of MAP2K6 polynucleotides normal, pre-neoplastic and neoplastic ovarian cell lines and ovarian surface epithelial cells obtained from patients(page 306, under the heading of "Cells and Cell Lines" in the presence and absence of hepatocyte growth factor (HGF) (Figure 1). In this case the candidate test agent is HGF.

The rejection of claims 1-6, 17, 19, 26-30 under 35 U.S.C. 102(b) as being anticipated by Stein et al (WO 97/22704) is maintained for reasons of record..

Claim 2 embodies the method of claim 1 wherein the assay system comprises a MAP2K polypeptide and the candidate test agent is a small molecule modulator. Claim 3 embodies the method of claim 2 wherein the screening assay is a kinase assay. Claim 4 embodies the method of claim 1, comprising a MAP2K polypeptide and an antibody as the candidate test agent. Claim 6 embodies the method of claim 5 wherein the nucleic acid modulator is an antisense oligomer.

Claim 17 is drawn to the method of clam 1 further com[rising (d) providing a second assay system comprising cultured cells, (e)contacting the second assay system with the test agent of (b) under conditions whereby but for the presence of the test agent, the system provides a reference activity; and (f)detecting an agent-biased activity of the second assay system, wherein

the second assay system includes a second assay that detects and agent-biased change in an activity associated with branching morphogenesis. Claim 19 embodies the method of claim 17 wherein the second assay system comprises cultures cells.

Claim 26 is drawn to a method comprising contacting a mammalian cell with an agent that specifically binds a MAP2K6 polypeptide or nucleic acid. Claim 27 embodies the method of claim 26 wherein the agent is administered to a mammalian animal predetermined to have a pathology associated with branching morphogenesis. Claim 28 embodies the method of claim 26 wherein the agent is a small molecule modulator, a nucleic acid modulator or a antibody. Claim 29 embodies the method of claim 26 wherein the branching morphogenesis is angiogenesis. Claim 30 embodies the method of claim 29 wherein tumor cell proliferation is inhibited.

It is noted that the phrase of claim 29, "wherein the branching morphogenesis is angiogenesis" and the phrase of claim 30 "wherein tumor cell proliferation is inhibited" are not given patentable weight when comparing the claims to the prior art as the phrases simply expresses the intended result of a process step positively recited, see MPEP 2111.04.

Stein et al disclose a method for identifying a composition which affects MEK6 activity comprising incubating said composition and MEK6 kinase or a polynucleotide encoding said kinase for a time sufficient to allow the components to interact ad measuring the effect of the composition of MEK6 kinase or the polynucleotide encoding the kinase, under conditions whereby but for the presence of the test agent, the system provides a reference activity and (c) detecting a test-agent biased activity of the assay system (claim 24, figures 4, 5 and 7a, column 12, lines 16-18). Stein et al disclose that test agent may include antibodies which neutralize MEK6, a competing peptide that represents the substrate binding domain of MEK6 or the dual phosphorylation motif of the MEK6 substrate, an antisense polynucleotide or ribozyme that interferes with the transcription or translation of MEK6, or a molecule that prevents transfer of phosphate groups from MEK6 to a substrate (page 7, lines 29-35). Stein et al disclose that ansiomycin treatment or exposure to UV light was able to activate MEK6 (page 24, lines 6-11) which fulfills the specific embodiment of "modulate". Stein et al disclose a second assay system comprising a coupled in vitro kinase assay to measure the activity of p38 in response to MEK6 (page 11, line 18 to page 12, line 36) which fulfills the specific embodiment of claim 17 with

respect to the second assay system. Stein et al disclose that antibodies and other agent having a desired effect on MEK6 activity may be administered to a patient to treat an existing disease in vivo, and that an agent which decreases MEK6 activity in vivo may be administered to treat inflammation, autoimmune diseases, cancer or degenerative diseases (page 17, lines 27-31) which fulfills the specific embodiment of claims 29-30.

Applicant argues that in order to anticipate the instant invention, Stein must teach a method of identifying a candidate branching morphogenesis modulating agent comprising the steps of providing an assay system comprising a MAP2K6 polypeptide or nucleic acid and contacting said assay system with a candidate composition under conditions wherein the presence of the test agent provides a reference activity and detecting the reference activity, wherein a difference between the test agent biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent. This has been considered but not found persuasive. As stated above,

the recitation of a method "of identifying a candidate branching morphogenesis modulating agent" and a "method for diagnosing a disease in a patient" has not been given patentable weight because said recitations occur in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone.

Further, as stated above,

the phrase "wherein a difference between the test agent-biased activity and the reference activity identifies the test agent as a candidate branching morphogenesis modulating agent" are not given patentable weight when comparing the claims to the prior art as it simply expresses the intended result of a process step positively recited.

Applicant argues that the contacting of a candidate agent with a MEK6 polypeptide and subsequently measuring the ability of the MEK6 polypeptide to activate p38 does not provide for the method of identifying a candidate morphogenesis modulating agent using an assay system comprising the MAP2KK6 polypeptide. However, this is not persuasive for the reasons set forth above.

Applicants arguments regarding the patentable weight of the preamble and wherein clauses are not persuasive (pages 14-16). this is not persuasive. Applicant cites *Catalina Marketing International Inc. v. Coolsavings.com Inc.*. It is noted that the case is concluded with the statement:

Because the district court erroneously relied on non-limiting language in the preamble [emphasis added] of Claim 1, this court vacates the district court's judgment of non-infringement of Claim 1, both literally and by equivalents, to give the district court the opportunity to construe the limitations of Claim 1.

Thus Catalina Marketing International Inc. v. Coolsavings.com Inc supports the non-reliance on language in the preamble.

Applicant also cites *Bell communications Research Inc., v Vitalink Communications Corp* and *Pitney Bowes, Inc., v Hewlette-Packard Co.* this has been considered but not found persuasive. In the instant case the preamble does not recite limitations of the claim, nor is it necessary to give life, meaning and vitality to the claim because the active method steps of the claim already have life, meaning and vitality in the context of the Stein reference.

Claims 1, 26-28, 30 and 31 are rejected under 35 U.S.C. 102(b) as being anticipated by Davis et al (WO 96/36642).

Claim 31 is drawn to a method comprising obtaining a biological sample from the liver, prostate, skin, stomach or testis of a patient; contacting said sample with a probe for MAP2K6 expression; and comparing the results with a control sample.

Davis et al disclose a method of identifying a subject at risk for a Map kinas kinase disorder by measuring activation of the MKK signal pathway which can be determined by measuring MKK synthesis (page 7, lines 3-7) which is commensurate with determining the level of expression of MKK (page 8, lines 7-9). Davis et al disclose that MKK-mediated disorders include various malignancies of the skin and liver (page 10, lines 1-7). Davis et al disclose that an MKK of the invention includes MKK6 (page 2, line 1).

Davis et al disclose that reagents found to inhibit MKK signal transduction pathways can be used as therapeutic agents for the treatment of MKK-mediated disorders (page 45, lines 1-3). Davis et al disclose that the method includes administration of an effective amount of a reagent that inhibits MKK function (page 45, lines 9-11). Davis et al disclose that reagents employed for the inhibition of MKK function or activity include polynucleotides, polypeptides and other molecules such as antisense oligonucleotides and ribozymes (page 46, lines 13-16) as well as antibodies and fragments thereof (page 46, lines 18-20). The disclosure of a ribozyme, antibodies including fragments as modulators of MKK meets the limitation of claim 28.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-6 and 17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704).

Claim 20 embodies the method of claim 17 wherein the second assay detects an event selected from a group including cell proliferation and cell cycling.

Stein et al teach that diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would measure cell proliferation and cell cycling.

It would have been prima facie obvious at the time the claimed invention was made to do an assay which would measure alterations in cell proliferation or cell cycling in conjunction with the second p38 assay. One of skill in the art would have been motivated to do so by the teachings of Stein et al on the diseases associated with the p38 cascade. One of skill in the art would understand based on the teachings of Stein et al that modulation of cell proliferation and modulation of cell cycling can result from modulation of p38 activity as a result of modulation of MEK6 activity.

Claims 1-6, 8-11 and 17-20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704)in view of Sodhi et al (Cancer Research, 2000, Vol. 60, pp. 4873-4880).

Claim 8 embodies the method of claim 1 wherein the assay system comprises cultured cells expressing MAP2K6 and wherein the system includes an assay that detects an agent-biased change in branching morphogenesis. Claim 9 specifies that said branching morphogenesis is angiogenesis. Claim 10 specifies that the assay system comprises cultured cells. Claim 11 embodies the method of claim 11 wherein the assay detects a response to hypoxic conditions. Claim 18 embodies the method of claim 17 wherein the second assay system detects an agent-biased change in an activity associated with angiogenesis. Claim 20 embodies the method of claim 19 wherein the second assay detects a response to hypoxic conditions.

Stein et al renders obvious the detection of modulation in cell proliferation and cell cycling as a result of modulation of p38 resulting from modulation of MEK6 for the reasons set

forth above. Stein et al do not teach or suggest the detection of an event which is a response to hypoxic conditions or angiogenesis.

Sodhi et al teach that both the MAPK pathway and the p38 pathway acts by modulating the phosphorylation state of HIF-1 in response to hypoxic conditions which results in the upregulation of VEGF and subsequent angiogenesis (page 4879, Figure 6). Sodhi et al teach that these finding provide the first insight into a mechanism whereby inflammatory cytokines and cellular stresses which activate p38 can interact with the hypoxia-dependent machinery of angiogenesis (abstract, last eight lines).

It would have been prima facie obvious at the time the claimed invention was made to measure the relative response of MEK6 and p38 to hypoxic stimuli by measuring angiogenesis. One of skill in the art would have been motivated to do so by the teachings of Sodhi et al which link the activation of MEK6 ((MKK6) and p38 to the activation of Hif-1alpha and subsequent angiogenesis.

Claims 1-6, 8, 9, 11,17, 19 and 20 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704) in view of Terada et al (Kidney International, 1999, Vol. 56, pp. 1258-1261).

Stein et al renders obvious the detection of modulation in cell proliferation and cell cycling as a result of modulation of p38 resulting from modulation of MEK6 for the reasons set forth above. Stein et al teach diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would cell cycling.

Terada et al teach that TGF-beta activates the TAK1-MKK6-p38 pathway and results in a transcriptional down-regulation of cyclin D1 (pages 1259-1260, under the heading of "Down-regulation of cyclin D1 Expression by the TAK1-MKK6-p38 Pathway").

It would have been prima facie obvious at the time the invention was made to measure cell cycling and cyclin D1 expression in the method of Stein et al. One of skill in the art would

have been motivated to do so by the teachings of Terada et al on the negative regulation of cyclin D1 by the MKK6-p38 pathway.

Claims 1-6, 8-13, 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704) in view of Matsumoto et al (Journal of Cell Biology, January 2002, Vol. 156, pp. 149-160).

Claim 11 embodies the method of claim 10 wherein the assay detects tubulogenesis. Claim 12 embodies the method of claim 10 wherein the assay detects tubulogenesis, and wherein the assay system comprises the step of testing the cellular response to stimulation with at least two different pro-angiogenic agents. Claim 13 embodies the method of claim 10 wherein the assay detects tubulogenesis and wherein the cells are stimulated with an inflammatory angiogenic agent. Claim 20 embodies the method of claim 19 wherein the second assay detects tubulogenesis. Claim 21 embodies the method of claim 20, wherein the assay detects tubulogenesis, and wherein the assay system comprises the step of testing the cellular response to stimulation with at least two different pro-angiogenic agents.. Claim 22 embodies the method of claim 20, wherein the assay detects tubulogenesis and wherein the cells are stimulated with an inflammatory angiogenic agent.

Stein et al teach that diseases associated with the p38 cascade include any disorder linked to MEK6 kinase activity including cell-growth related diseases such as cancer, metabolic diseases, abnormal cell growth and proliferation, or cell cycle abnormalities (page 13, lines 11-20). Stein et al teach the MEK6 assay coupled with the p38 kinase assay (above). Stein et al do not specifically teach an assay which would measure tubulogenesis and/or apoptosis along with the cellular response to at least two different pro-angiogenic agents.

Matsumoto et al teach that activation of p38 is induced by FGF-2 in endothelial cells undergoing tubular morphogenesis in culture, but that treatment with p38 inhibitors and dominant negative upstream regulators of p38 (such as dominant negative MKK6, page 152, first column, line 18 to second column, line 4) enhanced FGF-2 mediated tubular morphogenesis by regulating differentiation, apoptosis and proliferation of the endothelial cells (page 156, first paragraph under "Discussion"). Matsumoto et al teach that VEGF, which is proangiogenic in the chick chorioallantoic membrane did not activate p38 in vascular endothelial cells.

It would have been prima facie obvious at the time the claimed invention was made to extend the MEK6 and p38 coupled expression assays of Stein et al to measurement of tubulogenesis and apoptosis in the response of the assay system to the pro-angiogenic agents of FGF-2 and VEGF. One of skill in the art would have been motivated to do so by the teachings of Matsumoto et al linking the activation of p38 to the negative regulation of the tubulogenic response to FGF-2 and the induction of VEGF-mediated tubulogenesis without activation of p38. One of skill in the art would be motivated to determine if MKK6 was activated or not by FGF-2, and one of skill in the art would also be motivated to determine if a different kinase from MEKK6 controlled FGF-2 activation of p38. One of skill in the art would be motivated to include VEGF as a positive control for non-p38 modulated tubulogenesis.

Applicant argues against the above obviousness rejections stating that office action fails to provide explicit reasoning as to why Stein renders the claims obvious. Applicant again argues that Stein provides no teachings as to a link between MAP2K6 and branching morphogenesis and therefore one of skill in the art would not have been motivated to pursue the method using a second assay system. Applicant concludes that Stein only briefly mentions disease conditions associated with p38 in the completely unrelated context of using modulating agents for therapeutic purposes, and therefore one of skill in the art would have no motivation to use the assay in a method of identifying agents capable of modulating branching morphogenesis. Applicant argues that the supporting references fail to remedy this defect off the teachings of Stein. This has been considered but not found persuasive. As stated above,

the recitation of a method "of identifying a candidate branching morphogenesis modulating agent" and a "method for diagnosing a disease in a patient" has not been given patentable weight because said recitations occur in the preamble. A preamble is generally not accorded any patentable weight where it merely recites the purpose of a process or the intended use of a structure, and where the body of the claim does not depend on the preamble for completeness but, instead, the process steps or structural limitations are able to stand alone

It is noted that the motivation for combining of references need not be confined to those related to the modulation of branching morphogenesis. Section 2141 of the M.P.E.P. states

The reason or motivation to modify the reference may often suggest what the inventor has done, but for a different purpose or to solve a different problem. It is not necessary that the prior art suggest the combination to achieve the same advantage or result discovered by applicant.

Thus, one of skill in the art would have been motivated to combine the references to attain the active method steps as set forth above, without knowledge that the modulation of MAP2K6 was a modulator of branching morphogenesis.

Claims 1-7 are rejected under 35 U.S.C. 103(a) as being unpatentable over Stein et al (WO 97/22704) in view of Iversen (WO 00/24885). Claim 7 embodies the method of claim 6, wherein the nucleic acid modulator is a "PMO" (phosphorodiamidate morpholino oligomer).

Stein et al teach that test agent may include an antisense polynucleotide or ribozyme that interferes with the transcription or translation of MEK6 (page 7, lines 29-35). Stein et al do not specifically teach that the antisense polynucleotide is a phosphorodiamidate morpholino oligomer.

Iversen teaches that sterically hindered oligonucleotides, such as morpholino oligonucleotides are not associated with activation of RNAse and are therefore termed "RNase resistant" which reduces unwanted side effects relative to a non-modified "natural oligonucleotide" the inappropriate cleavage of non-target RNA heteroduplexes and binding to cellular proteins (page 7, lines 1-13).

It would have been prima facie obvious at the time that the claimed invention was made to use a phosphorodiamidate morpholino oligomer rather than a natural oligomer as the antisense agent taught by Stein et al. One of skill in the art would have been motivated to do so by the teachings of Iversen on the improvement afforded by using RNase resistant oligomers which avoid unwanted side effects of the natural unmodified oligomer by elimination of non-specific binding to cellular proteins and inappropriate cleavage of non-targeted RNA heteroduplexes.

Claims 1-13, 17-22, 26-31 are rejected.

Claims 15, 16, 24, 25, 34 and 35 are allowable.

All other rejections and objections as set forth or maintained in the previous Office action are withdrawn.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Karen A. Canella whose telephone number is (571)272-0828. The examiner can normally be reached on 10-6:30 M-F.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Larry Helms can be reached on (571)272-0832. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Karen A Canella/
Primary Examiner, Art Unit 1643